FAR-6721

4/18/84

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

006721

APR 18 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Mr. Robert Taylor, PM #25
Registration Division (TS-767C)

SUBJECT: EPA Registration No. 464-546, 464-554, 1F2508, 464-EUP-IE/4G3024.
Garlon 3A and Garlon 4A Herbicides for use on grasses, forage and hay. Request for tolerances in/on grasses, forage, hay, milk, meat and meat by-products, kidney and liver of cattle, sheep and goats.
Caswell No. 882I, Accession No. 070042, 070043, 070044, 252159, 072261

Reviewed by: William S. Woodrow, Ph.D.
Toxicology Branch (TS-769C)

FROM: Christine F. Chaisson, Ph.D.
Head, Review Section IV
Toxicology Branch (TS-769C)

Christine F. Chaisson 4/19/84
Rbfor WSW 4/18/84

PETITIONER: Dow Chemical Co.
Midland, MI 48460

Action Requested:

Dow Chemical Co. requests that the tolerances listed above be granted for the herbicides Garlon 3A and Garlon 4A. At present the Garlon products are registered by the Agency for control of woody plants and broadleaf weeds on rangeland, permanent grass pastures and non-crop areas, such as fence rows and around farm buildings.

Recommendations:

1. The requested tolerances can not be toxicologically supported.

2. The rat feeding/oncogenicity study is presently classified "Supplementary" and as such cannot be used to establish an ADI. This study could be upgraded if the information described by our staff pathologist, Dr. Louis Kasza, is provided to us by the registrant.

Review:

1. Section F

Permanent tolerances for combined residues o. 3,5,6-trichloro-2-pyridinyloxy-acetic acid, and . 3,5,6-trichloro-2-pyridinol and 2-methoxy-3,5,6-tric. are proposed as follows:

2000 ppm in or on forage grasses, hay.

Tolerances for combined residues of the herbicide triclopyr, 3,5,6-trichloro-2-pyridinyloxyacetic acid, and its metabolite, 3,5,6-trichloro-2-pyridinol:

0.5 ppm, of which no more than 0.2 ppm is triclopyr, in milk;

1.0 ppm, of which no more than 0.2 ppm is triclopyr, in meat, fat, and meat by-products except kidney and liver of cattle, goats, hogs, horses and sheep;

5.0 ppm, of which no more than 3 ppm is triclopyr, in liver and kidney of cattle, goats, hogs, horses and sheep.

2. Previously Submitted Toxicity Data

Acute Toxicity - Technical

Rat oral: LD_{50} (M) 713 mg/kg
LD_{50} (F) 713 mg/kg

Rat oral: LD_{50} (M) 729 mg/kg
LD_{50} (F) 630 mg/kg

Mouse oral: LD_{50} (M) 471 mg/kg

Cavies oral: LD_{50} (M) 310 mg/kg

Rabbit oral: LD_{50} (M & F) 550 mg/kg

Rabbit eye irritation: Slight corneal injury.

Rabbit skin irritation: Slight redness.

Rabbit dermal: LD_{50} > 2000 mg/kg

Acute Toxicity - Formulation:

Rat oral: LD_{50} (M) 2830 mg/kg
LD_{50} (F) 2140 mg/kg

...mage at , days.

...ion: Necrosis at 72 hours.

...ity - Metabolite (3,5,6-Trichloro-2-pyridinol)

Rat oral: LD_{50} (M) 794 mg/kg
LD_{50} (F) 870 mg/kg

Mouse oral: LD_{50} (M) 380 mg/kg
LD_{50} (F) 415 mg/kg

Acute Toxicity - Triclopyr as the ethylamine salt 44%

Rabbit eye irritation: No corneal opacity. Conjunctival irritation at day 1 (one animal), clear by day 2.

Acute Toxicity - Triclopyr as the butoxy-ethyl ester 1.15%

Rat oral: LD_{50} > 2 g/kg

Rabbit dermal: LD_{50} > 2 g/kg

Rabbit dermal irritation: 4 of 6 animals had edema at 24 hours, no irritation at 72 hours. P.I. = 0.1

Rabbit eye irritation: Conjunctival irritation in 9/9 at 24 hours, no irritation at 7 days.

Acute Toxicity - Triclopyr as the triethylamine salt 8.0%

Rat oral: LD_{50} (M) > 5 g/kg
LD_{50} (F) 6.4 g/kg

Rabbit dermal: No mortality at 5 g/kg.

Rabbit eye irritation: Conjunctival irritation at day 1, clearing by day 4.

Rabbit dermal irritation: Slight erythema - 1 animal at 24 hours, cleared by 48 hours.

Subacute Toxicity - Technical

Rat 90-day feeding: NOEL 30 mg/kg/day.

Rabbit teratology: NOEL > 100 mg/kg/day (HDT).

Rat teratology: NOEL > 200 mg/kg/day (HDT).
Fetotoxic NOEL 50 mg/kg/day.
Maternal NOEL < 50 mg/kg/day.

Rabbit teratology: NOEL>25 mg/kg/day (HDT).
Fetotoxic NOEL 25 mg/kg/day?

Effect on rabbit pregnancy: NOEL 25 mg/kg/day (HDT).

Monkey 28-day nasogastric intubation: NOEL 30 mg/kg/day (HDT).

Subchronic Toxicity - Technical

Rabbit pregnancy (effect of triclopyr)
NOEL 25 mg/kg/day (HDT).

Rat 3-generation reproduction: NOEL > 30 mg/kg/day (HDT).

Dog subchronic dietary feeding: No NOEL - LDT 5 mg/kg/day.

Dog supplemental subchronic dietary feeding: NOEL 2.5 mg/kg/day (HDT).

Mutagenicity Studies - Technical

Recombination repair assay: no repair effects.

Heritable translocation (interim report): negative

Mouse, host-mediated assay: negative

Rat, mammalian cytogenetic study: negative.

Rat, dominant lethal assay: weakly positive.

CF-1 mouse, dominant lethal assay: negative.

Rec-assay and reversion mutagenicity: negative.

Ames metabolic activation: no mutagenic potential.

Special Studies - Technical

Triclopyr pharmacokinetic profile - IV and oral administration, monkey: no significiant triclopyr accumulation.

Renal function studies, dog and monkey: monkey renal function unimpaired; 20 mg/kg/ day HDT, 5 mg/kg/day triclopyr reduced phenolsulfon-thalein excretion in dogs.

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Chronic Toxicity - Technical

CDF/COX mouse 2-year oncogenic study: not oncogenic in mice (240 ppm HDT).

Rat 2-year chronic toxicity/oncogenic study (IBT Report No. 621-06138, EPA Acc. No. 241901). Note: This IBT study has been validated and classified supplementary data; "a definitive statement relative to oncogenic potential cannot be based nor a NOEL for chronic toxicity be established on data from this study".

2. No new toxicity data were submitted.

3. At present, no tolerances have been established for Garlon 3A or for Garlon 4A

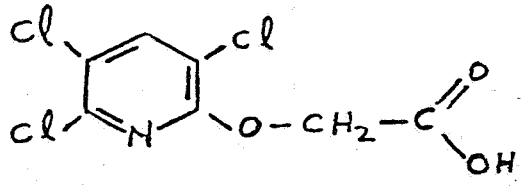
4. Substance identification:

Common name: Triclopyr

Chemical name: 3,5,6-Trichloro-2-pyridinyloxyacetic acid

Trademark: GARLON

Structural formula:



5. Garlon special toxicity concerns:

a. Comparisons of Garlon (triclopyr) metabolites in plants, the rat and goat.

A comparison of triclopyr metabolism in grass, the rat and goat reveals relatively comparable amounts of triclopyr and its metabolites 3,5,6-trichloropyridinol and 2-methoxy-3,5,6-trichloropyridine or conjugates of these compounds:

Posttreatment Assay	Identity and Amount
7 days (grass)	triclopyr and triclopyr conjugates - 35% 2-methoxy-3,5,6-trichloropyridine 12% 3,5,6-trichloro-2-pyridinol 0.1%
11 day feeding (goat)	urine -triclopyr - 66% glucuronide conjugate of pyridinol (after hydrolysis) - 34% milk - triclopyr 61% pyridinol 22% fat & tissue - 3,5,6-trichloropyridinol -58-87% triclopyr-trace to 15%
32 hours post single IV or oral dose (fat)	-(identification of radioactivity not complete) urine feces contained 86-96% of administered dose. For IV or oral doses, parent triclopyr and 3,5,6-trichloropyridinol comprise the major portion of radioactivity in urine.

b. Rabbit teratology study reviewed by Dr. D. G. Van Ormer (D. G. Van Ormer memo of 2/22/1982).

Dr. Van Ormer's conclusions stated that Garlon did not demonstrate teratogenic properties; however, "the study fails to show a no-effect level for fetotoxicity: minor anomalies and increased normal variants."

According to the tester, Huntingdon Research Laboratory report, statistical analyses for minor skeletal anomalies and variant sternbrae show that no significant differences were found between controls and the low or high animal test groups; 10 or 25 mg/kg/day, respectively, at $p > 0.05$, using the pair-wise Wilcoxon test.

At Woodrow's request, Dow Chemical reworked the original data using:

A Kruskal-Wallis ANOVA, and;

The Gehan-Wilcoxon tests. Their findings agreed with the original tester's findings; that a fetotoxic NOEL = 25 mg/kg/day, at $p > 0.05$. Herbert Lacayo, Tox. Branch Statistician, checked the Dow statistical analysis of fetus minor skeletal anomalies and variant sternbrae; Mr. Lacayo agreed that there are no differences between controls and test animals at the low or high doses (10 or 25 mg/kg/day) when analyzed at $p > 0.05$. Thus, a fetotoxicity NOEL for triclopyr for this rabbit teratology study is 25 mg/kg/day.

c. Incidence of pulmonary adenomas in mice treated with triclopyr.

Woodrow's August 11, 1983, memorandum (Garlon) stated that a definite increase in pulmonary adenomas occurred at all dose levels during a 2-year mouse oncogenic study; a definite increase at all dose levels in male mice (24, 80 and 240 ppm) and a statistically significant increase in pulmonary adenomas in female mice at the HTD (240 PPM).

Dow Chemical (Woodrow's August 11, 1983, memo) replied that one of the parent mouse strains (BALB/C) used to produce the CDF mouse used in the triclopyr oncogenic study has a documented spontaneous tumor incidence of about 25%, and that Tox. Branch should have allowed concurrent study control mice (not actually the study controls) to be included in the statistical analysis of pulmonary adenoma incidence.

Dr. Louis Kasza of Tox Branch in a December 27, 1983, memo (attached) reevaluated the incidence of lung tumors in CDF/COX mice treated with Garlon (Triclopyr) and concluded that "the oncogenic potential of Garlon can not be substantiated" or, stated differently, Garlon did not demonstrate oncogenic potential in the CDF/COX mouse during a 2-year oncogenic study.

6. Calculation of the ADI

For consideration of the requested Tolerances, we could consider a provisional ADI (pADI). The pADI is based on a NOEL of 2.5 mg/kg/day in the 6-month dog Supplemental Subchronic Dietary Feeding Study in Beagle Dogs (HDT) for this study. A NOEL for the previously performed Subchronic Dietary Feeding Study in Beagle Dogs could not be established; dogs receiving 5, 10, or 20 mg/kg/day exhibited toxicological symptoms at all dose levels, thus an LEL for this (the first 6-month subchronic Dietary Dog Feeding study) is 5 mg/kg/day. The submitted 2-year rat feeding/oncogenicity study was classified supplemental, therefore an ADI could not be established using the rat data. A 100-fold safety factor is used to calculate the pADI.

$$\text{p ADI} = 2.5 \text{ mg/kg/day} \times \frac{1}{100} = 0.0250 \text{ mg/kg/day}.$$

The MPI for a 60 kg person is 1.5000 mg/day.

7. The current tolerances for Garlon are the first to be proposed. The current action utilizes 25.42 % of the pADI.

8. Infant exposure to Garlon resulting from 100 % milk diet.

a. Infant: 8 kg X 1 liter/kg

.2 ppm tol. X 1 = $\frac{0.2}{8}$ = 0.025 mg/kg/day = pADI

b. Another method of calculating infant exposure:

0.77 kg milk X 0.2 ppm tol. = 0.154

$\frac{0.154}{4}$ = 0.0385 mg/kg/day = 1.54 pADI

The infant milk exposure calculated by method a. is equal to the calculated adult exposure; however, the infant exposure calculated by method b. (above) slightly exceeds the adult exposure.

Conclusions and Recommendations:

Significant consumption of agriculture commodities to be treated with Garlon is expected, as evidenced by the large TMRC. Neither the 6-month dog subchronic feeding study, nor the rat chronic study meet minimum standards, and are not adequate to establish an ADI. Therefore, the requested tolerances cannot be toxicologically supported.

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ACCEPTABLE DAILY INTAKE DATA

Dog mg/kg	NOEL ppm	S.F.	PADI mg/kg/day	MPI mg/day (60kg)
2.500	100.00	100	0.0250	1.5000

Current Action 1F2508

CROP		Tolerance	Food Factor	mg/day (1.5kg)
Milk & Dairy Products	(93)	0.500	28.62	0.21461
Meat, red	(90)	1.000	10.81	0.16219
Kidney	(203)	5.000	0.03	0.00225
Liver	(211)	5.000	0.03	0.00225

MPI		TMRC	%PADI
1.5000 mg/day	(60kg)	0.3813 mg/day (1.5kg)	25.42

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